## REMARKS & CONCLUSION

The above-listed claim amendments along with the following remarks are fully responsive to the Final Office Action of April 4, 2006 and the Advisory Action of June 22, 2006. Claims 28-31 are amended. New claims 33-37 are added. No new matter is added by the amendments. Claims 28-37 are pending.

**Claim Rejections – 35 U.S.C. § 112, 1st paragraph**

Claims 28-32 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Advisory Action of 6/22/06 asserted that there is inadequate disclosure for selecting all four framework regions of both the heavy and light chain variable domains that are selected from different human antibodies.

Applicants respectfully submit that the previously pending claims contained no limitation that required selecting all four framework regions of both the heavy and light chain variable domains from different human antibodies. In fact, it is not excluded from the claim scope that at least two framework regions could be selected from the same human antibody. To further clarify this, the claims have been amended to recite that the framework regions of the light chain and the framework regions of the heavy chain are each selected from at least one human antibody, wherein the framework regions of the light and heavy chains are selected from different human antibodies. Support for this method is found in at least Example 1 and Figure 1, where the framework regions of the variable domains of the heavy chain are selected from two different human antibodies, namely EU and NEWM. The framework regions of the variable domains of the light chain is from REI. Applicants respectfully submit that methods of humanization of monoclonal antibodies, wherein the framework regions of the light and heavy chains are selected from different human antibodies, is nowhere disclosed in the cited prior art.

Example 1 further provides written description for claims 29 and 34, which recite that the framework regions are selected from at least three different human antibodies. Example 1 discloses selection of framework regions from EU, NEWM and REI, which are clearly three

different human antibodies. As discussed below, the motivation for selection of framework regions from at least three different human antibodies is not part of the claim limitations.

The Advisory Action of 6/22/06 also asserted that there is inadequate written support of the selection of the heavy chain having a sequence identity of at least 62.5% or higher and framework regions of the light chain having a sequence identity of at least 69% or higher. Applicants respectfully traverse this rejection. Example 1 and Figure 1 clearly discloses the residue identity for the light chain of 69.5% for framework 1, 80% for framework 2, 71.9% for framework 3 and 72.7% for framework 4. The residue identity for the heavy chain is 76.7% for framework 1, 71.4% for framework 2, 62.5% for framework 3 and 90.7% for framework 4. Figure 1 clearly provides the written description support for the sequence identities of at least 62.5% for the framework regions of the heavy chains and at least 69% for the framework regions of the light chains. The Office Action of 4/4/06 stated at page 6, 1st paragraph that, "the selected human framework regions of the light chain are 69% for FR1, 72% for FR3 and 72% for FR4 (Figure 1 and legend) and the selected human framework regions of the heavy chain are 73%, 71% and 62.5% for FR1-3, respectively." It is unclear why the Advisory Action concluded that numbers of 69%, 72% and 72% did not support, "at least 69%" or that numbers of 73%, 71% and 62.5% fail to support "at least 62.5%." Clearly, 73% and 71% are higher than 62.5%.

Furthermore, as one of skill in the art would recognize, the higher the homology, the more successful the method of humanizing a non-human monoclonal antibody. Applicants have shown in Example 1 that an amino acid residue identity range lower than 75-92.3% in some framework regions also resulted in successful humanization. Notably, an amino acid residue identity as low as 62.5% in some framework regions also resulted in successful humanization. The skilled artisan reading Example 1 would reasonably believe that if a sequence identity as low as 62.5% may, in some cases, result in a usable humanized antibody, then a higher range would be even more likely to result in a usable humanized antibody. As indicated above, there is explicit support for the successful humanization of 71% and 73% residue identity.

The Advisory Action of 6/22/06 also indicated no written description support for selecting all four framework regions of both the heavy and light chain variable domains that are selected from different human antibodies because in the case of the heavy chain, selection

of the NEWM was used for framework 4 because of the lack of X-ray coordinate data for the EU sequence.

Applicants note that the previously pending and amended claims do not recite any limitations that ascribe a specific motivation for each step of the claimed methods. There is no recitation of "selecting framework regions from at least two different human antibodies when X-ray coordinate data is missing." Rather, the claims recite a series of steps to be followed to perform the claimed method. The question of written description concerns whether or not there is adequate disclosure to support those recited steps, not whether or not a motivation is provided to the skilled artisan for each step in the method. As amended, the claims recite selecting framework regions from at least one human antibody for the light chain and at least one different human antibody for the heavy chain. Those steps are clearly supported by the specification, which discloses selection of framework regions from EU and NEWM for the heavy chain and REI for the light chain. REI is a different antibody from EU and NEWM.

Claim 30 recites the method of claim 28, wherein the heavy chain framework regions are selected from at least two different human antibodies. The Specification discloses selection of heavy chain framework regions from EU and NEWM. EU and NEWM are two different human antibodies. It is irrelevant that framework 4 X-ray data was missing for EU. Again, claim 30 does not recite a motivation for the selection of heavy chain framework regions from at least two different human antibodies. Such a selection may be made for a variety of reasons. For example, the heavy chain of a given mouse monoclonal antibody may show high homology for FR1 and FR2 from the heavy chain of one human antibody and low homology for FR3 and FR4, with high homology for FR3 and FR4 from the heavy chain of a different human antibody. The existing X-ray data may indicate high steric interference for FR1 from one human antibody variable chain and low steric interference for FR2, FR3 and FR4, while indicating low steric interference for FR1 from a different human antibody variable chain. There are a variety of considerations that may be taken into account in selecting FR sequences from one or more human antibodies. For example, Example 1 (Paragraph 0067) of the Specification states that, "the human REI (FIG 1A, SEQ ID NO:6) and EU (FIG. 1B, SEQ ID NOS. 9 and 10) sequences were found to exhibit the highest degree of sequence homology to the FRs of the VK and VH domains of LL2, respectively." This

selection of different human antibodies (REI and EU) for different framework regions was based on homology, not missing X-ray data.

As presently amended, but not entered, the claims recite that the selection of the amino acid sequences is from "human antibodies" and not "human monoclonal antibodies." Support for this amendment can be found through the Specification and at least at paragraphs [0043] and Example 1.

The Advisory Action stated that the new matter rejection could be obviated by removing the limitations to specific homology ranges from the claims. While Applicants traverse the assertion that the recited homology range limitations were new matter, new claims 33-37 are added herein without the recited homology ranges in order to advance prosecution of the application.

For the reasons stated above, Applicants assert that the Specification provides written description support for the claimed subject matter. Withdrawal of this rejection is respectfully requested.

**Claim Rejections – 35 U.S.C. § 112, 2nd paragraph**

Claims 28-32 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Office Action of 4/4/06 indicated that claim 28 is indefinite because it is not known whether both heavy and light chain variable domains of a monoclonal antibody are humanized and whether the heavy and light chain variable domains of the monoclonal antibody to be humanized are compared to only the heavy chain variable domain or only the light chain variable domains of two or more human antibodies.

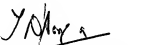
Claim 28 is amended to recite amino acid sequences of "the light and heavy chain variable domains," which indicates that the variable domains of both the heavy and light chains are humanized by comparing them to their corresponding variable domains of both the heavy and light chains in two or more human antibodies. Support for the amendment may be found in the Specification at least in Examples 1-4.

Applicants respectfully request withdrawal of this rejection.

**Conclusion**

In light of the amendments and remarks herein, Applicants respectfully request entry of this paper. If there are any remaining questions, the Examiner is requested to contact the undersigned at the number listed below.

Respectfully Submitted,

By: 

Tanya S. D'Souza, 56,948
612/766-7835
Customer No. 35657

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